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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,017	03/02/2004	Maik Obendorf	2877	1212

7590 10/18/2006  
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EXAMINER

HOWARD, ZACHARY C

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/791,017	Applicant(s) OBENDORF ET AL.	
	Examiner Zachary C. Howard	Art Unit 1646	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 July 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 3-8, 12, 13, 19-22, 26, 27 and 31-35 is/are pending in the application.
- 4a) Of the above claim(s) 12, 13, 19-22, 26 and 27 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 34 and 35 is/are allowed.
- 6) ☒ Claim(s) 3-8, 31 and 33 is/are rejected.
- 7) ☒ Claim(s) 32 is/are objected to.
- 8) ☒ Claim(s) 3-8, 12, 13, 19-22, 26, 27 and 31-35 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 May 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/26/2006</u> | 6) <input type="checkbox"/> Other: _____  |

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## DETAILED ACTION

### ***Status of Application, Amendments and/or Claims***

The amendment of 5/26/06 has been entered in full. Claims 3, 5, 6 and 8 are amended. New claims 32-35 are added.

Claims 12, 13, 19-22, 26 and 27 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 1/11/2005.

Claims 3-8 and 31-35 are under consideration.

### ***Information Disclosure Statement***

The Information Disclosure Statement of 5/26/06 has been considered.

### ***Priority***

The certified English translation of U.S. Provisional Application 60/465,692 submitted with the 5/26/06 response is considered sufficient to establish priority for the instant application to the filing date (April 25, 2003) of the provisional application.

### ***Withdrawn Objections and/or Rejections***

The following page numbers refer to the previous Office Action (12/20/05).

The objections to the specification at pg 4-5 are *withdrawn* in view of Applicants' amendments to the specification.

The objection to claims 5 and 8 at pg 6 is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 3-5 under 35 U.S.C. § 112, first paragraph at pg 6-9 for failing to provide enablement for methods of screening with fragments is *withdrawn* in view of Applicants' persuasive arguments and further consideration of the Examiner. (It is noted that cancelled claim 11 was inadvertently included in this rejection).

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The rejection of claims 3-8 and 31 under 35 U.S.C § 112, second paragraph, at pg 9-10 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn in part* in view of Applicants' amendments to the claims. The portion of the rejection that is maintained is set forth in the section "Claim Rejections – 35 USC § 112, 2<sup>nd</sup> paragraph".

***Maintained Objections and/or Rejections***

***Claim Rejections - 35 USC § 112, 1<sup>st</sup> paragraph***

Claims 6-8 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening comprising a full-length Ewing sarcoma protein of SEQ ID NO: 2 and a full-length human androgen receptor, does not reasonably provide enablement for methods of screening with fragments of said proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection was set forth at pg 6-9 of the 12/20/05 Office Action for claims 6-8; new claim 33 is herewith included in this rejection.

Applicants' arguments (5/26/06) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response dated 5/26/06, Applicants submit that, with respect to fragments, the claims are limited to a single sequence with respect to each protein; i.e., residues 325-918 of the androgen receptor (AR) and 319-656 of Ewing sarcoma protein (EWS). Applicants submit that the specification teaches that said fragments bind to each other in a yeast two-hybrid assay. Applicants argue that one of skill in the art could use said assay to screen test substances to identify substances that alter said binding. Applicants argue that the interaction of the C-terminal region of AR is consistent with other results from the literature. Applicants submit an IDS with seven reference that show that the C-terminal region of AR can interact by itself with other proteins and that "one reason for this is that the LBD binding domain, which is part of the fragment, is necessary for ligand binding, for example for transcription" (pg 26).

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Applicants' arguments have been fully considered and are found persuasive *in part*. The Examiner agrees with Applicants' argument that the fragments of AR and EWS could be used in a yeast two-hybrid assay to identify test substances that alter the binding between the two fragments. Therefore, the rejection of claims 3-5 has been withdrawn as indicated in the section "Withdrawn Claim Objections and/or Rejections".

However, Applicants' arguments are not persuasive with regard to the transcriptional assays encompassed by claims 6-8 and 33. A yeast two-hybrid assay only requires interaction between two proteins or protein fragments. In contrast, the transcription assay encompassed by claims 6-8 and 33 requires activation of target gene transcription by the AR in response to binding the ligand androgen, with the EWS protein as a co-activator. Applicants' only working example of the transcription assay (pg 20 and Figure 4) uses both full-length EWS and full-length AR. Fragments of the proteins involved in this process will not necessarily function as the full-length protein. As set forth previously, the relevant art teaches that amino acids 141-338 of AR are necessary for full ligand-inducible transcriptional activity (see pg 176 of Heinlein, et al. *Endocrine Reviews*. 23(2): 175-200; cited previously). The fragment recited by Applicants in claim 6 (residues 325-918) contains only 13 amino acids of this critical domain of AR. Second, even with a full-length AR, it is unpredictable whether amino acids 319-656 of EWS are sufficient to act as a co-activator of AR-mediated transcription. While this fragment is sufficient for binding, it is unpredictable whether or not it is sufficient to act as a co-activator. Residues 1-318 represent almost half of the entire EWS protein and deletion of this much of the protein will have an unpredictable effect on the ability of the EWS protein to act as a co-activator of AR-mediated transcription. The relevant art teaches the unpredictability and complexity with regard to making changes (including deletions) within the amino acid sequence of a protein that do not alter the functionality of the protein (Wells, 1990; Ngo et al, 1995; Bork, 2000; Skolnick and Fetrow, 2000; Doerks *et al.*, 1998; Smith and Zhang, 1997; Brenner, 1999; Bork and Bairoch, 1996; all cited previously). Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill

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in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid deletions), and the nature and extent of changes that can be made in these positions. The full-length proteins contain significantly more amino acids than the fragments, and each residue may contribute to the three-dimensional structure of the protein that influences binding and transcription-activating properties of the complex.

The Examiner has considered the seven references submitted by Applicants on the 5/26/06 IDS. These references support the use of fragments of the androgen receptor (AR) in yeast two-hybrid assays, but not in assays of androgen-receptor stimulated transcription. For example, Wang et al (2001), uses the ligand-binding domain of AR in a yeast two-hybrid assay (pg 40418), but uses full-length AR and full-length co-activator (ARA267- $\alpha$ ) in transcription assays (pg 40420). Furthermore, Fujimoto (1999) states, "The N-terminal region is involved in transcriptional activation of AR" (pg 8316).

Applicants have stated that the claims are limited to methods of using a single fragment of AR (325-918) and a single fragment of EWS (residues 319-656). However, the claims are directed to methods of using proteins comprising said fragments. Therefore, the genus of encompassed proteins actually includes all fragments of AR that comprise residues 325-918 and all fragments of EWS comprising residues 319-656. Therefore, the claimed methods encompass a large number of fragments that may need to be tested for transcriptional activity by the skilled artisan. It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether or not the method of the present invention could be used to determine the hormonal effect of substances using the recited fragments of EWS and/or AR. There are no examples of AR-mediated transcription activity using fragments of EWS and AR. Thus the specification fails to teach the skilled artisan how to use the method for screening without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method for the above stated purpose.

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As set forth previously, due to the large quantity of experimentation necessary to determine if the method could be used for screening, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

Claims 3-8 and 31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection was set forth at pg 9 of the 12/20/2005 Office Action.

In the 5/26/06 response, Applicants submit that the amino acid sequence of Genbank AAA51775 used in the examples has been submitted as SEQ ID NO: 8 and is included in new dependent claims 32 and 33 (but not independent claims 3 and 6).

Applicants' arguments have been fully considered but are not found persuasive. As set forth previously, claims 3 and 6 refer to residues 325-919 of human androgen receptor but do not clearly indicate the specific sequence in which these residues are found. Human androgen receptors are polymorphic in length and each polymorphic receptor comprises a different sequence of amino acids as residues 325-919. Therefore, the identity of residues 325-919 in the claims is indefinite because the specific androgen receptor sequence has not been identified. The remaining claims (claims 4, 5, 7, 8 and 31) are rejected for depending from an indefinite claim.

***New Objections and/or Rejections***

***Claim Objections***

Claim 32 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

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**Conclusion**

Claims 34 and 35 are allowed.

Applicants' amendment necessitated the new objection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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